REMARKS

The undersigned attorney gratefully acknowledges the courtesies extended by Examiner Spear and Examiner Ware during the personal interview conducted at the United States Patent and Trademark Office on March 21, 2002.

I. Status of the Claims

Claims 1-34 are pending. Claims 1-3 and 22-26 have been amended. Support for the amendments to claims 1-3 are found in the original specification as filed, e.g., at page 4, lines 12-15; Support for the amendment to claim 22 is found in the original specification as filed, e.g., at page 28, table 1; support for the amendment to claim 23 is found in the original specification as filed, e.g., at page 30, table 3; support for the amendment to claim 24 is found in the original specification as filed, e.g., at page 35, table 6; support for the amendment to claim 25 is found in the original specification as filed, e.g., at page 32, table 5; support for the amendment to claim 26 is found in the original specification as filed, e.g., at page 28, table 1. It is respectfully submitted that no new matter has been added by virtue of this amendment.

II. Information Disclosure Statement

In the Office Action, it was indicated that the Information Disclosure Statement filed on September 19, 2001 did not comply with 37 C.F.R. 1.98(a)(2). As discussed during the interview, it appears that the cited references became disassociated with the file and copies of the references cited in the Information Disclosure Statement will be resubmitted by hand delivery.

III. Rejections Under 35 U.S.C. § 112

In the Office Action, claims 4-31 were rejected as being indefinite on the grounds that "claims 4-31 require the method of claim 3, however claim 3 is a composition claims." In response, claim 3 has been amended to properly recite a method.

In the Office Action, claims 22-26 were rejected as being indefinite on the grounds that the claims are "omnibus type claims." In response, claims 21-25 have been amended as not to make reference to the Figures of the application.

In view of the actions taken, it is respectfully requested that the rejections under 35 U.S.C. § 112 be withdrawn.

IV. Rejections Under 35 U.S.C. § 102 and 35 U.S.C. § 103

In the Office Action, claims 1-15 and 19-34 were rejected as being anticipated and obvious over WO 00/28989 ("Lewis et al."), on the grounds that Lewis et al. "discloses controlled release metformin compositions [and] does not explicitly disclose the functional limitations of the instant claims, however since the formulations of [Lewis et al.] are substantially the same, it appears that the instant claimed functional limitations are inherent within [Lewis et al.]"

Claims 1-15 and 19-34 were rejected as being anticipated and obvious over U.S. Patent No. 5,955,106 ("Moeckel et al."), stating that Moeckel et al. "is relied upon for the same reasons set forth in the [Lewis et al.] rejections".

Claims 1-15 and 19-34 were rejected as being anticipated and obvious over WO 99/47125 ("Cheng et al."), on the grounds that Cheng et al. "is relied upon for the same reasons set forth in the [Lewis et al.] rejections ... [and Cheng et al.] discloses a semi-permeable membrane coating surrounding the core."

Claims 16-18 were rejected on the grounds of obviousness over the Lewis reference, the Moeckel reference or the Cheng reference, in view of Drug Facts and Comparisons (1999) which "is relied upon for teaching delivery of metformin in the presence or absence of food."

With respect to rejections under the doctrine of inherency, it is noted that as set forth in the MPEP, 8th edition, section 2122, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be recognized by one of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

It is further set forth in the MPEP, 8th edition, section 2122 that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to

reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. And Inter. 1990) (emphasis in original).

Further, as discussed during the interview, the Federal Circuit stated the following in *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268-69, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991):

> *Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.*

In view of the above discussion on the doctrine of inherency, the references cited by the Examiner are discussed below:

THE CHENG REFERENCE

The rejection of claims 1-15 and 19-34 on the grounds of anticipation and obviousness over WO 99/47125 ("Cheng et al.") is respectfully traversed as the Cheng reference has not been fully considered in its entirety.

As stated at page 3, lines 14-17 and at page 4, lines 6-9 of the Cheng reference, the formulations disclosed therein provide a controlled or sustained release formulation for an antihyperglycemic drug that obtain peak plasma levels approximately 8-12 hours after administration. Therefore, the administration of formulations which provide a T_{max} of the agent at from 5.5 to 7.5 hours after administration as recited in the present claims cannot be inherent by the administration of formulations disclosed in the Cheng reference. Further, the Cheng reference does not provide motivation to one skilled in the art to modify the formulations therein to obtain a T_{max} of the agent other than that which is specifically taught in the reference, i.e., a T_{max} of 8 to 12 hours.

In view of the arguments presented, the Examiner is respectfully requested to remove the anticipation and obviousness rejections over the Cheng reference.

THE LEWIS REFERENCE

The rejection of claims 1-15 and 19-34 on the grounds of anticipation and obviousness over WO 00/28989 ("Lewis et al.") is respectfully traversed.

As set forth in the MPEP, 8th edition, section 2112.02, under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior ar6t device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it cab be assumed that the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 19867).

The exemplified formulations of the Lewis reference are Examples 1-7 on pages 10-12. Example 1 describes a single or bilayer tablet comprising 4 or 8 mg of Compound I (an insulin sensitizer) and 1000 to 1500 mg of metformin HCl coated with an enteric coating of Eudragit L30 D-55, triethyl citrate and talc Alphafil 500 in the described percentages; Example 2 describes the single or bilayer tablets of Example 1 coated with a semi-permeable membrane of Eudragit RS30D, triethyl citrate and talc in the described percentages; Example 3 describes a non-disintegrating matrix single layer tablet of Compound I, metformin HCl and the described excipients in the described amounts, and a bilayer tablet to provide sustained release of Compound I and immediate release of metformin HCl with the described excipients in the described amounts; Example 4 describes a single and trilayer tablet of Compound I and metformin HCl with the described excipients in the described amounts; Example 5 describes a single layer tablet of Compound I and metformin HCl with the described excipients in the described amounts; Example 6 describes a single and bilayer tablet of Compound I and metformin HCl with the described excipients in the described amounts; and Example 7 describes a capsule containing multiple pellet cores having Compound I, metformin HCl with the described excipient in the described amounts.

The examples of the present specification teach formulations which comprise a core comprising metformin or a salt thereof, a membrane surrounding the core, and at least one passageway in the membrane, the formulations providing a mean T_{max} from 5.5 to 7.5 hours after administration. Given the benefit of the information provided by the present specification, one skilled in the art would be able to modify other controlled release technologies in order to achieve these pharmacokinetic parameters.

As demonstrated above, the examples of the present application and the examples of the Lewis reference are directed to different controlled release technologies by virtue of their different ingredients, structure and methods of manufacture and it cannot be assumed that the prior art formulation would inherently perform the claimed method. Accordingly, a *prima facie* case of anticipation or obviousness based on inherency has not been established in the Office Action as there has not been provided a basis in fact and/or technical reasoning to reasonably support the determination that the prior art formulation would necessarily perform the method claimed.

Further, the Office Action has not taken into account the fact that there is no teaching in the Lewis reference to administer a formulation to arrive at the claimed T_{max} as recited in the present claims, nor does Lewis provide any motivation to one skilled in the art to achieve this parameter using the formulations described therein. In fact, it is respectfully submitted that as Lewis is silent as to the T_{max} of their formulations, one skilled in the art would be motivated to administer a formulation to achieve a T_{max} from an antihyperglycemic agent controlled release formulation which is known in the art, (e.g., a T_{max} of 8-12 hours as taught in the Cheng reference). It is pointed out that the present claims do not recite an all encompassing range of T_{max}, but rather a particular subset which is not taught or obvious over the prior art.

In view of the arguments presented, the Examiner is respectfully requested to remove the anticipation and obviousness rejections over the Lewis reference.

THE MOECKEL REFERENCE

The rejection of claims 1-15 and 19-34 on the grounds of anticipation and obviousness over U.S. Patent No. 5,955,106 ("Moeckel et al.") is respectfully traversed.

At the very least, the Moeckel reference does not teach or suggest administration of the formulations described therein on a once-a-day basis as recited in the present claims.

Further, the same arguments set forth above with respect to the Lewis reference are applicable to the Moeckel reference.

The exemplified formulations of the Moeckel reference are Examples 1-7 on columns 5-9 of the patent. Example 1 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose,

Macrogol and titanium dioxide in the specified amounts; Example 2 describes a process of preparing a formulation with a core of metformin hydrochloride, hydroxyethylcellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropyl-cellulose, lactose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 3 describes a process of preparing a formulation with a core of metformin hydrochloride, sodium carboxy methyl cellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 4 describes a process of preparing a formulation with a core of metformin hydrochloride, polyacrylic acid, methylhydroxypropylcellulose, and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; Example 5 describes a process of preparing a formulation with a core of metformin hydrochloride, hydroxypropyl-cellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of poly(ethylacrylate-methylacrylate, talcum and anti-foaming agent in the specified amounts; Example 6 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts; and Example 7 describes a process of preparing a formulation with a core of metformin hydrochloride, methylhydroxypropylcellulose, polyvidone and magnesium stearate in the specified amounts with a film envelope of methylhydroxypropylcellulose, ethylcellulose, Macrogol and titanium dioxide in the specified amounts.

As set forth above, the Examples of the present specification teach formulations which comprise a core comprising metformin or a salt thereof, a membrane surrounding the core, and at least one passageway in the membrane, the formulations providing the claimed pharmacokinetic parameter of a mean T_{max} from 5.5 to 7.5 hours after administration.

Accordingly, the examples of the present application and the examples of the Moeckel reference are directed to different controlled release technologies by virtue of their different ingredients, structure and methods of manufacture. Accordingly, a *prima facie* case of anticipation or obviousness based on inherency has not been established as the Office Action has not provided a basis in fact and/or technical reasoning to reasonably support the determination

that the prior art formulation would necessarily perform the method claimed.

Further, the Office Action has not taken into account the fact that there is no teaching in the Moeckel reference to arrive at the claimed T_{max} as recited in the present claims, nor does Moeckel provide any motivation to one skilled in the art to achieve this parameter using the formulations described therein. In fact, it is respectfully submitted that as Moeckel is silent as to the T_{max} of their formulations, one skilled in the art would be motivated to achieve a T_{max} from a biguanide controlled release formulation which is known in the art, (e.g., a T_{max} of 8-12 hours as taught in the Cheng reference). As stated above with respect to the Lewis reference, it is pointed out that the present claims do not recite an all encompassing range of T_{max}, but rather a particular subset which is not taught or obvious over the prior art.

In view of the arguments presented, the Examiner is respectfully requested to remove the anticipation and obviousness rejections over the Moeckel reference.

DRUG FACTS AND COMPARISONS

The rejection of claims 16-18 on the grounds of obviousness over the Lewis reference, the Moeckel reference or the Cheng reference, in view of Drug Facts and Comparisons (1999) is respectfully traversed.

This rejection is respectfully traversed as this reference fails to cure the deficiencies of the Lewis reference, the Moeckel reference and the Cheng reference as presented above. Namely, Drug Facts and Comparisons does not provide motivation to achieve a method of administering an antihyperglycemic formulation to provide a mean T_{max} from 5.5 to 7.5 hours of the agent after administration

V. Double Patenting Rejections

Claims 1-34 were provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-42 of copending application serial number no. 09/705,630.

In response, in order to expedite the issuance of a patent, a terminal disclaimer is submitted herewith over this copending application. Applicants note that the obviation of an obvious-type double patenting rejection by the filing of a terminal disclaimer is not an admission, acquiescence, or estoppel on the merits of an issue of obviousness. *See Quad Environmental*

Technologies Corp. v. Union Sanitary District, 946 F.2d 870, 873-74, 20 U.S.P.Q.2d 1392, 1394-95 (Fed. Cir. 1991).

Claims 1-34 were rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-29 of U.S. Patent no. 6,099,859; claims 1-39 of U.S. Patent No. 6,284,275; claims 1-4 of U.S. Patent No. 6,099,862. In the Office action, it was stated with respect to each reference that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to limitations that are in a genus-species relationship and the functional limitations of the instant claims would be inherent in [the reference]." Further, claims 1-34 were provisionally rejected under obviousness type double patenting as being unpatentable over claims 1-54 of copending application no. 09/594,637 and over claims 1-29 of copending application no. 09/726,193 on the grounds that "the method claims disclose the compositions".

These rejections are respectfully traversed. It is submitted that the claimed pharmacokinetic parameter of a mean T_{max} of 5.5 to 7.5 hours after administration as recited in the present claims are not obvious in view of the claims of the cited references. As discussed during the interview, although formulations encompassed by the claims of these references may provide a T_{max} of between 5.5 to 7.5, the claimed pharmacokinetic parameters do not necessarily flow from formulations encompassed by these claims. Therefore, the Examiner is requested to remove these rejections.

VI. Conclusion

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
Patents, Trademarks and Copyrights
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

Version With Markings To Show Changes Made

IN THE CLAIMS

The following claim has been amended as follows:

1. (Amended) A method for lowering blood glucose levels in human patients needing treatment for non-insulin-dependent diabetes mellitus (NIDDM), comprising orally administering to human patients on a once-a-day basis at least one oral controlled release dosage form comprising an effective dose of at least one suitable antihyperglycemic agent or a pharmaceutically acceptable salt thereof and a controlled release carrier, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) of [metformin] the agent at from 5.5 to 7.5 hours after administration.

2. (Amended) The [controlled release dosage form] method of claim 1 wherein said at least one antihyperglycemic agent is a biguanide.

3. (Amended) The [controlled release dosage form] method of claim 2 wherein said biguanide is metformin or a pharmaceutically acceptable salt thereof.

22. (Amended) The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml [a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 1], based on administration of a 1700 mg once-a-day dose of metformin after an evening meal.

23. (Amended) The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean $AUC_{0-\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml [a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 2], based on administration of a 2000 mg once-a-day dose of metformin after an evening meal.

24. (Amended) The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml [a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 4], based on administration of a 2000 mg once-a-day dose of metformin after an evening meal [at dinner].

25. (Amended) The method of claim 3, in which the administration of the at least one metformin dosage form provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration [a mean plasma concentration-time profiles of metformin substantially as set forth in FIG. 6], based on administration of a 2000 mg once-a-day dose of metformin after an evening meal [at breakfast].

26. (Amended) The method of claim 22 [3], in which the administration of the at least one metformin dosage form provides a mean $T_{1/2}$ from 2.8 to 4.4 [about mean plasma glucose concentration-time profiles substantially as set forth in FIG. 5, based on administration of a 2000 mg once-a-day dose of metformin at dinner].